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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/205,658	12/03/98	RUVKUN G	00786/351004

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KAREN L ELBING
CLARK & ELBING
176 FEDERAL STREET
BOSTON MA 02110

EXAMINER	
KAUSHAL,S	
ART UNIT	**PAPER NUMBER**
1633	9

DATE MAILED: 01/10/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/205,658	RUVKUN et al
Examiner	**Group Art Unit**
SUMESH KAUSHAL	1633

☒ Responsive to communication(s) filed on *Oct 28, 1999*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-5, 8-23, 25, and 26* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-5, 8-23, 25, and 26* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's, remarks and the Dr. Gary Ruvkun deceleration, each filed 10/28/99, as responsive to the earlier official action, mailed 5/27/99 has been considered. Claims 6-7 and 24 are canceled. Claim 3-23, 25 are amended and a newly filed claim 26 is entered. Claims 1-5, 8-23, 25-26 are pending in this application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

1. Claim 25 is objected to because of the following informalities: The instant claim depend upon a canceled claim (claim 24). Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. Claims 1-5, 8-23, 25-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, **to make and/or use the invention.**

Applicant's arguments and the Dr. Gary Ruvkun deceleration filed on 10/28/99 have been fully considered but they are not fully persuasive in view of rejections below.

3. The instant claims are drawn to a method for identifying a compound that modulates the expression or activity of DAF-18, DAF-18 mutant gene or DAF-18 human homologue (PTEN) gene in a cell or a transgenic nematode or mouse, by contacting a cell or administering a transgenic animal with the candidate compound, which increases or decreases the DAF-18 activity. The claims are also drawn to identify a candidate compound that modulates the DAF-18 activity and is capable of treating an impaired glucose tolerance condition or obesity and longevity of a cell or organism. The claims are further drawn to identify a compound capable of ameliorating or delaying an impaired glucose tolerance condition or obesity and increasing the longevity of a cell or organism by contacting a biological sample with candidate compound and assaying the sample for DAF-18, DAF-18 mutant or PTEN mediated lipid phosphatase activity. The claims are also drawn to a method of diagnosing an impaired glucose tolerance condition or obesity and longevity in a patient by analyzing the level of PTEN expression or activity in a sample isolated from the patient. Furthermore, claims are also drawn to a method of ameliorating or delaying the onset of an impaired glucose tolerance condition or obesity and increasing longevity in a patient by administering a therapeutically effective amount of a compound that modulates the PTEN expression or activity. In addition, claims are drawn to a transgenic nematode encoding a mammalian PTEN polypeptide wherein the animal carries a mutation in a DAF-18 gene.

4. The specification fails to provide guidance for a method for identifying a compound that modulates the expression or activity of DAF-18, DAF-18 mutant gene or DAF-18 human homologue (PTEN) gene in a cell or a transgenic nematode or mouse, by contacting a cell or administering a transgenic animal with the candidate compound, which increases or decreases the DAF-18 activity.

The specification fails to describe the regulatory regions of nematode DAF-18 and human PTEN gene promoters. The disclosure of the DAF-18 and PTEN genes and its promoter are considered essential because the claims are drawn to a method for the identification of a compound that is capable of modulating the expression of a DAF-18 and PTEN gene in a cell or a mutant transgenic nematode or a mouse. Applicants argument on pages 15-17 which states that "it is not necessary ... that expression of a PTEN or DAF-18 polypeptide be directed by its endogenous promotor" are not persuasive because the compounds identified by claimed method are used to treat impaired glucose tolerance, obesity and/or longevity in all animals, including mammals. Although, an exogenous promotor, for example C. elegans ins-1 or daf-16 can be used to regulate the expression of a gene of interest, it is not useful to identify the compound that modulates daf-18 or human PTEN activity because compounds are for the modulation of exogenous promoters (ins-1 or daf-16) and not for the endogenous def-18 or human PTEN regulatory region. Furthermore, it is not clear how the compound identified which modulate the expression of an exogenous promoter would modulate the activity of daf-18 or PTEN gene in-vivo.

5. The specification fails to make and use any transgenic nematode or a mouse expressing DAF-18 gene, DAF-18 mutant gene or the human PTEN gene. The specification fails to show that a genomic DNA fragment encoding the DAF-18 or human PTEN homolog is introduced in a nematode or a mouse to obtain the required phenotype of transgenic animals. The claims are read in the light of specification to identify a compound by using a transgenic mouse or a nematode, whose germ cells or somatic cells contain a transgene encoding for a DAF-18, PTEN polypeptide wherein the transgene includes a knockout mutation (see page 14, lin.2). The state of the art at the time of filing was such that transgene expression and the physiological results of such an expression in animals of different species could not be accurately predicted because cis elements are controlled differently by various transacting factors in the genome of different species (Well, Theriongenology 45:57-68, 1996; see

page 61, par.3). Considering the unpredictability in transgenic art, the specification fails to teach the required phenotype of any and all nematodes or mouse encoding def-18 or human PTEN gene. The specification teaches that def-18 and PTEN exhibits sequence homology and fails to demonstrate that these genes have similar function. It is well know in the art that even conservative amino acid substitution or deletion in a polypeptide adversely effects the activity of the polypeptide. In addition, the art at the time of filing was such that interaction among various DAF genes in C. elegans is complex (Larsan et al, Genetics 139:1567-1583, 1995; see page 1573 fig-1). The specification provides no correlative teachings as to the interaction and effect of human PTEN gene with other DAF genes in a nematode cellular/genetic environment. It is not clear how a transgenic cells or animals encoding PTEN would be used to identify compounds capable of treating impaired glucose tolerance, obesity and longevity.

6. Applicant's arguments filed on 10/28/99, page 7 and the Dr. Ruvkun's deceleration have been fully considered but they are not persuasive because they fail to point out where in the specification there is guidance for any and all compounds capable of increasing the expression or activity of the DAF-18 or human PTEN genes, which are capable of treating impaired glucose tolerance, obesity and longevity. The claims when read in the light of specification, embrace the identification of compounds that are capable of treating the impaired glucose tolerance, obesity and longevity by modulating the expression/activity of daf-18 and human PTEN gene in a cell and/or transgenic animals

7. The specification states that insulin signaling pathway can regulate dauer arrest from nervous system and may regulate aging from nervous system in mammals (see page 102, lin 20, App. Spec.). Although, longevity and diapause control is unique to C. elegans it is also an essential feature of many vertebrates or in vertebrates and the DAF-2 signaling is analogous to mammalian longevity increase

associated caloric restriction (see page 103, lin 9, lin 16, App. Spec.). However, the specification fails to show that any DAF-gene is associated with the onset of impaired glucose tolerance, obesity and longevity in other animals, especially mammals. The state of the art at the time of filing was such that various factors governs the development of impaired glucose intolerance or obesity. The mechanism underlying the development of obesity are complex and are not well understood. Obesity is a complex phenotype which is not only the result of genetic variations but is also the out come of personal behavioral and life style (Lonnqvist et al Nat. Med. 1(9):950-953, 1995, see page 951 col.1 para.1 line 1). Furthermore, the development of impaired glucose intolerance involves both hyperlipidemia and the dietary fat composition which also depends upon personal dietary habits (Zeman et al, Atherosclerosis, 134(1-2):318, 1997). Moreover, without clear correlation that DAF-18 and PTEN results in impaired glucose tolerance, obesity or increased longevity, there is no enablement for the claimed method of identifying compounds. The instant specification provides no guidance to achieve the modulation of def-18 or human PTEN gene in a nematode or a mouse which leads to impaired glucose tolerance, obesity and increased longevity.

8. The therapeutic use of a compound that modulate longevity in C.elegans is not enabled for human patients because there are considerable evolutionary and environment differences between humans and C. elegans. The state of the art at the time of filing was such that when food is scarce, a reversible arrest of development is triggered in C. elegans leading to the development of metabolically less active dauer larval stage which exhibit a marked increase in longevity that is also affected by the temperature (Kimura et al, Science 277: 942-946, 1997; see page 942 col.1, par.1. Larsan et al, Genetics 139:1567-1583, 1995; see page 1577, table-4) However, the effect of caloric restriction on aging in humans is more complex because the process of ageing in humans is not only governed by various etiological factors but is also influenced by the industrialized world, modern hygiene and health care facilities (Austad, Neurobiology of Ageing 16(5):851-852, 1995, see page

851 col.2 par.3). On the other hand role of PTEN and its interaction with other DAF human homologs is not know in the art. Neither the specification nor the art at the time of filing, teaches that DAF-18 and human homolog PTEN are involved in the regulation of longevity in human and nematodes. Furthermore, specification fails to show that a genomic DNA fragment encoding the human PTEN homolog could rescue the inherent defects of DAF-18 (e1375) mutant alleles in C. elegans.

9. The applicant argues that a diabetic insulin resistant patient carries a mutation in an insulin receptor similar to DAF-2 gene of C.elegans but fails to demonstrate the role of the claimed daf-18 and PTEN gene in any and all patients with impaired glucose tolerance or with atherosclerosis or obesity. Applicant's arguments and the Dr. Ruvkun's deceleration are not persuasive because they fail to point out where in the specification or deceleration there is guidance for "clear association between daf-genes (daf-18 and human PTEN) and the onset of impaired glucose tolerance conditions associated obesity" (page 3, para.7 deceleration). Similarly, the specification is not enabled for a method of diagnosing an impaired glucose tolerance condition or obesity and longevity in a patient by analyzing the level of PTEN expression or activity in a sample isolated from the patient because the role of PTEN in the above mentioned conditions is not clear.

Furthermore, as set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific

Thus, in view of the lack of guidance in the specification and unpredictability in the art, the skilled artisan at the time of filing would have had to engage in undue experimentation to identify compounds for the treatment of impaired glucose tolerance, obesity and longevity related to daf-18 and human PTEN expression. The quantity of experimentation required would have included the isolation and use of def-18 and human PTEN promotor and regulatory regions, making of transgenic nematodes and mouse wherein the daf-18 or PTEN homologs are knocked out and exploration of the role of def-18 and human PTEN in the development of impaired glucose tolerance condition, obesity and longevity in humans.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned as (703) 308-2035. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

Sumesh Kaushal
Art Group 1633

JOHN L. LeGUYADER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600